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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/742,684	12/19/2000	Lawrence S. Mathews	SALK1720-6	2857

7590 03/23/2004

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EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/742,684	MATHEWS ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 18-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 18-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

I. Status of Application, Amendments, and/or Claims

The amendment filed on January 12, 2004 has been entered and Applicants' argument in response to the communication mailed on December 8, 2003 has been considered and found to be persuasive because the nucleic acid sequence of SEQ ID NO: 15 encodes the elected amino acid sequence of SEQ ID NO: 16. Therefore, the amendment filed on September 26, 2003 has been entered in full. Claims 12 and 13 have been canceled. Claim 11 has been amended. Claims 18-36 have been added. Claims 11 and 18-36 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

II. Claim Rejections under 35 USC § 112, 1st Paragraph, Scope of enablement

(i) The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(ii) Claims 11, 21, and 27-34 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a screening method of using a vertebrate activin receptor set forth in SEQ ID NO: 2, 4, or 16, does not reasonably

provide enablement for a screening method of using a genus of vertebrate activin receptors or soluble polypeptides with undefined amino acid sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The breadth of the claims. Claim 11 is drawn to a method for screening a collection of compounds to determine those compounds which bind to receptors of activin/TGF-β superfamily, said method comprising employing a vertebrate activin receptor in a competitive binding assay, wherein said vertebrate activin receptor is encoded by a nucleotide sequence which is (a) the nucleotide sequence of a cDNA mlecule present in a vertebrate library, wherein the noncoding strand of the cDNA molecule *hybridizes under conditions of low stringency* with a probe comprising the contiguous sequence of nucleotides 128-1609 of SEQ ID NO: 15; or (b) a sequence degenerate with the sequence of a cDNA molecule according to (a). Claim 21 depends from claim 11. Claim 27 is drawn to the same method as that of claim 11,

except claim 21 requires employing a soluble polypeptide, rather than a vertebrate activin receptor. Claims 28-34 depend from claim 27, either directly or indirectly. Thus, the claims are so broad that they encompass a screening method of using *a genus of vertebrate activin receptors or soluble polypeptides with undefined amino acid sequences.*

Nature of the invention and the state of the prior art. The present invention is related a method of screening for compounds that bind to a vertebrate activin receptor using a competitive binding assay. Given a receptor polypeptide, an artisan can skilfully practice a competitive binding assay and a screening method. At the effective filing date of the application, a number of activin receptors were shown to exist, for example, Kondo et al. identified two types of specific receptor for activin/EDF expressed on Friend leukemia and embryonal carcinoma cells (*Biochem. Biophys. Res. Commun.* 161:1267-1272, 1989). Campen et al. has also characterized activin A binding sites on human leukemia cell line K562 (*Biochem. Biophys. Res. Commun.* 157:844-849, 1988). However, the vertebrate activin receptors had not been cloned and the cDNA sequences had not been reported in the art.

The amount of direction or guidance presented and the existence of working examples. Despite the fact that the instant disclosure provides sufficient guidance on how to make the mouse, xenopus, and human activin receptors set forth in SEQ ID NOS: 2, 4, and 16, and use these receptors in the method of screening for those compounds that bind to the vertebrate activin receptors, the specification fails

to provide sufficient direction or working example on how to make other vertebrate activin receptors encoded by cDNA molecule that hybridizes, *under conditions of low stringency,* with the nucleic acid sequence of SEQ ID NO: 15 (which encodes the human activin receptor of SEQ ID NO: 16). This is because under conditions of low stringency, any nucleic acids would hybridize or simply stick to the nucleic acid sequence of SEQ ID NO: 15. There is no sufficient direction provided to guide an artisan to make a nucleic acid encoding a polypeptide that shares significant sequence homology with SEQ ID NO: 16 and retains the functions of the human activin receptor of SEQ ID NO: 16. Furthermore, there is no sufficient directions or examples provided to guide an artisan to make a soluble polypeptide and to practice the method of screening for compounds that bind to receptors of activin/TGF- β superfamily using the soluble polypeptide.

The relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary. Although one skilled in the art certainly has the technology and skills to practice a screening method, it is unpredictable whether a polypeptide encoded by a nucleic acid that hybridizes under conditions of low stringency would retain the same function as that of the human activin receptor. The state of the art is such that determining the specificity of hybridization is empirical by nature and the effect of mismatches is unpredictable, as taught by Wallace et al. (Methods Enzymol. 152:432-443, 1987) and Sambrook et al. (Molecular Cloning, A Laboratory Manual, 2nd Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, page 11.47). It is well known in the art that

hybridisation, in particular under conditions of low stringency, yields structurally unrelated nucleic acids molecules. A soluble polypeptide encoded by a nucleic acid hybridising under conditions of low stringency with SEQ ID NO: 15 may have entirely different structure and activity from that of the human activin receptor.

Furthermore, the state of the art (See, e.g., Ngo, et al, *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz, et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495) is such that the relationship between sequence of a protein and its activity is not well understood and is not predictable. Excising out portions of a protein or modifications to a protein, e.g., by substitutions or deletions, would often result in deleterious effects to the overall activity and effectiveness of the protein.

Therefore, in view of the nature of complexity of the work and unpredictability of the art, it would require undue experimentation for one skilled in the art to make the genus of vertebrate activin receptors or soluble polypeptides with undefined amino acid sequences and to use the claimed screening method commensurate in scope with these claims without sufficient guidance and/or working examples on how to produce a functional vetebrate activin receptor or a soluble polypeptide encoded by a nucleic acid hybridizing with SEQ ID NO: 15 under low stringency.

III. Claim Rejections under 35 USC § 112, 1st Paragraph, Written Description

Claims 11, 21, and 27-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claim 11 is drawn to a method for screening a collection of compounds to determine those compounds which bind to receptors of activin/TGF-β superfamily, said method comprising employing a vertebrate activin receptor in a competitive binding assay, wherein said vertebrate activin receptor is encoded by a nucleotide sequence which is (a) the nucleotide sequence of a cDNA mlecule present in a vertebrate library, wherein the noncoding strand of the cDNA molecule hybridizes under conditions of low stringency with a probe comprising the contiguous sequence of nucleotides 128-1609 of SEQ ID NO: 15; or (b) a sequence degenerate with the sequence of a cDNA molecule according to (a). Claim 21 depends from claim 11. Claim 27 is drawn to the same method as that of claim 11, except claim 21 requires employing a soluble polypeptide, rather than a vertebrate activin receptor. Claims 28-34 depend from claim 27, either directly or indirectly. Thus, claims 11 and 21 are drawn to a screening method of using a genus of vertebrate activin receptors with undefined amino acid sequences, whereas claims 27-34 are drawn to a screening method of using a genus of soluble polypeptides with undefined amino acid sequences.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics,

structure/function correlation, methods of making the claimed product, or any combination thereof.

In the instant case, claim 11 only requires that the vertebrate activin receptor be encoded by a cDNA which hybridizes with SEQ ID NO: 15 at low stringency. The claims do not require that the vertebrate activin receptor or its encoding nucleic acids possess any particular conserved structure or other disclosed distinguishing feature. To make it even worse, claim 27 does not even require that the polypeptide is a vertebrate activin receptor and there is no recitation of any structural or functional limitations. It is well known in the art that hybridization at low stringency would yield nucleic acids that may be structurally unrelated. The specification describes vertebrate activin receptors from mouse, xenopus, and human, as set forth in SEQ ID NOS: 2, 4, and 16, but fails to disclose a representative number of species of the recited genus. It is further noted that the recitation of "a vertebrate activin" does not suffice to define the genus because it is only an indication of what the genus does, rather than what it is.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of the vertebrate activin receptors or their encoding nucleic acids.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making it. The compound itself is required.

Therefore, only the receptors described in the instant application, but not the full breadth of the activin receptors or their encoding nucleic acids meets the written description provision of 35 U.S.C. §112, first paragraph. Accordingly, only the screening method of using the activin receptors specifically disclosed in the specification meets the written description provision of 35 U.S.C. §112, first paragraph.

IV. Claim Rejections under 35 USC § 112, 2nd Paragraph

The rejection of claim 11 under 35 U.S.C. 112, 2nd paragraph, as set forth at page of 4-5 of the previous office action (Paper No. 18, June 26, 2003), is maintained.

New claims 18-36 are also rejected under 35 U.S.C. 112, 2nd paragraph on the same basis.

Applicants argue that the claim has been amended to address the Examiner's concerns and to specify the use of a vertebrate activin receptor in the binding assay. Applicants' argument has been fully considered, but is not deemed to be persuasive because the preamble of the claim still recites "a method for screening a collection of compounds to determine those compounds which bind to receptors of the activin/TGF superfamily". However, the steps set forth in the method do not necessarily screen compounds which bind to receptors of the activin/TGF-β superfamily because, as pointed out in the previous office action, a compound that binds to an activin receptor

does not necessarily bind to a TGF-β receptor (Kondo et al, *Biochem. Biophys. Res. Commun.* 161:1267-1272, 1989; also see the bottom of page 8 of specification).

Furthermore, new claim 27 requires the use of a soluble polypeptide in the screening method. A compound that binds to a soluble polypeptide does not necessarily bind to a TGF-β receptor because there is no recitation of the functional limitation for the soluble polypeptide.

V. Claim Rejections under 35 USC § 102(b)

The rejection of claim 11 under 35 U.S.C. 102(b) as being anticipated by Kondo et al, (*Biochem. Biophys. Res. Commun.* 161:1267-1272, 1989) is maintained.

New claims 21, 27, and 31 are also rejected as being anticipated by Kondo et al. on the same basis.

Applicants argue that the amended claim 11 requires the use of a specific vertebrate activin receptor encoded by nucleotide sequences hybridizing to specific nucleotide regions of SEQ ID NO: 15. In contrast, Kondo only shows the existence of a receptor tht has activin-binding activity on cultured cells, but does not isolate, sequence, or further characterize any such receptor. Therefore, Kondo does not teach or suggest a method for screening a collection of compounds employing a vertebrate activin receptor as claimed.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, the method recites the use of a genus of vertebrate activin receptors, not a specific one, as Applicants have argued. The

sequence of the recited vertebrate activin receptor is undefined because the recited vertebrate activin receptor is encoded by nucleic acids, which hybridize under *conditions of low strigency* with nucleotides 128-1609 of SEQ ID NO: 15. It is well known in the art that hybridization, in particular undr conditions of low stringency, would yield structurally unrelated nucleic acid molecules.

Secondly, the limitation to vertebrate activin is analogous to "a product by a process". In this regard, it is noted that a product made by a new process does not distinguish a product that is already known in the art. In the instant case, whether the vertebrate activin receptor is made by recombinant DNA technology or by chemical synthesis does not effectively limit the scope of the invention because the method simply recites a vertebrate activin receptor and the amino acid sequence of the receptor is undefined. Since Kondo et al. teach a method of identifying compounds that bind to a mouse activin receptor in a competitive assay, the reference of Kondo et al. meets the limitations of the claim.

Finally, the mouse activin receptor expressed in Friend leukemia is necessarily encoded by a nucleic acid sequence, and the nucleic acid sequence encoding the activin receptor would, by its nature, hybridize to SEQ ID NO: 15 under conditions of low stringency. The instant application also discloses two mouse activin receptors, in addition to the human activin receptor of SEQ ID NO: 16. There is no evidence that the nucleic acid encoding the mouse activin receptor expressed in Friend leukemia cells would not hybridize at low stringency to SEQ ID NO: 15.

VI. Claim Objection

The objection to claim 11 is maintained because the amended claim 11 recites "a vertebrate activin receptor", which encompasses unelected subject matter, i.e., vertebrate activin receptors other than the elected human activin receptor set forth in SEQ ID NO: 16. New claims 18-24 and 27-34 are also objected to for the same reason. Appropriate correction is required.

VII. Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Ruixiang Li
Examiner
March 11, 2004

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SUPERVISORY PATENT EXAMINER
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